REMARKS

This Amendment, filed in reply to the Office Action dated April 20, 2011, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Claims 1, 2, 4, 11-37 and 40-42 are all the claims pending in the Application. Claims 1, 11, 12 and 14-37 are withdrawn from consideration as allegedly being directed to non-elected inventions. Claims 2, 4, 13 and 40-42 are rejected. Claim 2 is amended herewith solely to correct antecedent basis.

No new matter is added by way of this Amendment. Entry and consideration of this Amendment are respectfully requested.

Withdrawn Rejections

1. Applicants thank the Examiner for withdrawal of the rejection of Claims 2, 4, 13 and 40-42 under 35 U.S.C. § 112, second paragraph.

2. Applicants thank the Examiner for withdrawal of the rejection of Claims 2, 4, 13 and 40-42 under 35 U.S.C. § 103.

Claims 2, 4, 13 and 40-42 are Definite Under 35 U.S.C. § 112, 2nd Paragraph

On page 3 of the Office Action, Claims 2, 4, 13 and 40-42 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Specifically, the Examiner contends that there is insufficient antecedent basis for recitation of "said patient" in Claim 2.

Solely to expedite prosecution, Claim 2 is amended herewith to replace the recitation of "said patient" with "said subject." Applicants respectfully submit that the amendment overcomes the rejection.

Withdrawal of the rejection is respectfully requested.

Claims 2, 4, 13 and 40-42 are Enabled Under 35 U.S.C. § 112, 1st Paragraph

On page 4 of the Office Action, Claims 2, 4, 13 and 40-42 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement.

In justifying the rejection, the Examiner contends that the state of the art at the time of the invention - regarding the correlation of particular SNPs to particular disease phenotypes - was highly unpredictable. Based on this alleged unpredictability, the Examiner purports that those of skill in the art would need to experiment unduly in order to diagnose, or predict susceptibility to, open angle glaucoma based on the presence of the claimed polymorphisms.

To support this allegation of unpredictability, the Examiner cites to Lucentini *et al.* (*The Scientist*, 2004, 18:1-3) who allegedly discloses that "it is strikingly common for follow-up studies to find gene-disease associations wrong … when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding." The Examiner also cites to Tabor *et al.* (*Nature Reviews Genetics*, 2002, 3:1-7) for a similar proposition, stating that Tabor *et al.* discloses that "significant findings of association in many candidate gene studies have not been replicated when followed up in subsequent association studies." The Examiner also cites Wacholder *et al.* (*J. Natl. Cancer* Inst., 2004, 96:434-442) for the proposition that proffered associations between polymorphisms and disease states often turn out to be false, even when statistical significance is found.

Applicants respectfully disagree, and traverse the rejection in view of the following remarks.

As noted above, this lack of enablement rejection is predicated on alleged unpredictability in the art regarding the correlation of particular SNPs to particular disease phenotypes. Applicants, however, respectfully submit that this broad conclusion of unpredictability, based essentially on the disclosures of Lucentini *et al.*, Tabor *et al.*, and Wacholder *et al.*, is on the whole, inapplicable to the associations discovered by Applicants, and such would be recognized by those of skill in the art.

For example, Applicants note that Lucentini *et al.* ascribe the irreproducibility of many gene associations to a trend in the art for "[n]ew high throughput analysis techniques … [which] let researchers study many gene-disease associations quickly and cheaply … [and] also lead to more studies on associations that don't look especially likely at a study's outset. This tends to increase the likelihood of finding spurious links through chance occurrences." (Emphasis added.) *See* page 4, 1st paragraph, of Lucentini *et al.*

Indeed, Applicants respectfully note that Lucentini *et al.*, in the very next paragraph, suggests that such spurious associations could be prevented by factoring in the probability of a particular gene having a true role in a particular association, prior to the study. As such, any reliance on Lucentini *et al.*, as alleged evidence of unpredictability as to whether the claimed polymorphisms actually correlate with open-angle glaucoma, is inapt. That is, Lucentini *et al.* attributes the irreproducibility of many gene polymorphism associations to high-throughput analysis, which test a plethora of genes for which "associations … don't look especially likely at a study's outset." In contrast, however, Applicants have not embarked on the type of high-

throughput analysis suggested by Lucentini *et al.* as being responsible for spurious associations to discover the associations of the present invention.

In this regard, Applicants note that myocilin, for instance, is highly expressed within the eye (the physical site of open-angle glaucoma), and the art has recognized over fifty different mutations in this gene that are associated with glaucoma development.[1] Thus, unlike the studies subject to criticism in Lucentini *et al.*, which test a plethora of genes for which "associations … don't look especially likely at a study's outset," myocilin is both highly, and specifically, expressed in the area affected by glaucoma, and the art recognizes that mutations in myocilin are associated with glaucoma. Similarly, noelin-2 is expressed at the relevant site, in the retina,[2] and has significant structural, and by implication functional, similarity to myocilin. That is, the claimed SNPs occur within genes for which a logical association with the disease state is present - they are specifically expressed at the site at which open-angle glaucoma occurs.

Turning to Wacholder *et al.*, also cited in the rejection as alleged evidence of unpredictability, Applicants note that Wacholder *et al.* discloses unpredictability in essentially the same context - the drawing of correlations based on "testing several haplotypes and SNPs in thousands of genes whose functions remain obscure or unknown," *see* page 434, column 2, of Wacholder *et al.*, resulting from "technical advances, including lower cost, reductions in quantity

[1] *See* Funayama *et al.* (*Investigative Opthalmology & Visual Science*, 2006, 47(12):5368-5375). In accordance with M.P.E.P. 609.05(c), this document is being submitted as evidence directed to an issue raised in the Office Action, and no fee pursuant to 37 C.F.R. 1.97 or 1.98, or citation on a FORM PTO/SB/08 or PTO-1449 is believed to be necessary.

[2] *See* Tomarev *et al.* (*Investigative Opthalmology & Visual Science,* 2003, 44:2588-2596). In accordance with M.P.E.P. 609.05(c), this document is being submitted as evidence directed to an issue raised in the Office Action, and no fee pursuant to 37 C.F.R. 1.97 or 1.98, or citation on a FORM PTO/SB/08 or PTO-1449 is believed to be necessary.

of DNA required, [and] high throughput platforms." *Id.* That is, Wacholder *et al.* provides no more support for the rejection than does Lucentini *et al.*, and similarly fails as alleged evidence of unpredictability as to whether the claimed polymorphisms correlate with open-angle glaucoma.

In addition, Applicants respectfully note that any unpredictability alleged to be established by Tabor *et al.* is equally inapplicable to the claimed invention. Although Tabor *et al.* is relied upon as evidence that many candidate-gene studies have yielded correlations that have not been successfully repeated, citing page 1, column 3 - Tabor *et al.* subsequently explains that failure to detect the SNP in future experiments is often due to differences in the study design, such as in the study population or the definition of the phenotype. *See* page 2, column 3, 1st paragraph of Tabor *et al.*

Moreover, and like Lucentini *et al.*, Tabor *et al.* emphasizes that this lack of repeatability may be explained by the selection of polymorphisms "that are not likely to be causal … [but are] selected because of the ease of genotyping." That is, all the references cited in the rejection to support unpredictability with regard to the correlation of particular SNPs to particular disease phenotypes, emphasize that such unpredictability results from high-throughput analyses using genes without a known, predicted, or logical association. In contrast, however, Applicants respectfully submit that those of skill in the art would recognize the correlations discovered by Applicants not to be spurious and irreproducable, at least because myocilin and noelin-2 are specifically and highly expressed at the disease site, numerous mutations in myocilin have been associated with glaucoma, and because noelin-2 is structurally, and thus by implication functionally, related to myocilin.

In addition to the above, Applicants respectfully note that Tabor *et al.* also indicates that "variants in coding regions - specifically non-synonymous and nonsense variants, frameshift variants and variants in splice sites - are the least common types of polymorphism … variants in non-coding regions and coding-region variants that do not change the amino acid sequence are more frequent in the population. [This] support[s] the contention that it is reasonable to place the highest priority for genotyping on variants that result in changes to the amino-acid sequence, because these variants are most likely to affect the function of the protein, and to be involved in disease aetiology." (Emphasis added.) *See* page 5, 2nd column, 1st paragraph, of Tabor *et al.* Accordingly, Applicants respectfully submit that Tabor *et al.* is even more irrelevant in view of this, given that both of the claimed polymorphisms change the coding sequence, and thus the structure of the resulting protein.

Moreover, that it would not require undue experimentation to diagnose, or predict susceptibility to, open angle glaucoma based on the presence of the claimed polymorphisms is further supported by Funayama *et al.*, a copy of which is attached herewith for the Examiner's convenience.[3] For example, Funayama *et al.* discloses the conservation of Arg144 in noelin-2, even amongst highly diverse animal species. This, taken with the fact that the claimed noelin-2 SNP was not identified in any control individual, only reaffirms the validity of this correlation. Further, with respect to the Phe369Leu myocilin SNP presently claimed, the art-recognized association between myocilin SNPs and open angle glaucoma (and the expression at the site at which the disease occurs) strongly supports the validity of this correlation.

[3] In accordance with M.P.E.P. 609.05(c), this document is being submitted as evidence directed to an issue raised in the Office Action, and no fee pursuant to 37 C.F.R. 1.97 or 1.98, or citation on a FORM PTO/SB/08 or PTO-1449 is believed to be necessary.

In view of the foregoing, Applicants respectfully submit that it would not require undue experimentation to practice the invention as claimed.

Withdrawal of the rejection is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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